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UNIVERSITY OF SOUTHERN CALIFORNIA

COMMUNICATION

The European Patent Office herewith transmits

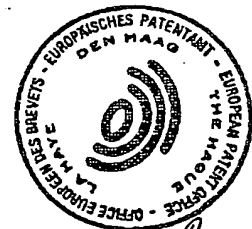
- ☐ the European search report
- ☐ the declaration under Rule 45 EPC
- ☐ the partial European search report under Rule 45 EPC
- ☒ the supplementary European search report concerning the international application under Article 157(2) EPC relating to the above-mentioned European patent application. Copies of the documents cited in the search report are enclosed.

The following specifications given by the applicant have been approved by the Search Division :

- ☐ Abstract ☐ Title ☐ Figure
 - ☐ The abstract was modified by the Search Division and the definitive text is attached to this communication.
 - ☐ The following figure will be published with the abstract, since the Search Division considers that it better characterises the invention than the one indicated by the applicant.
- Figure:
- ☐ Additional copy(copies) of the documents cited in the European search report.

REFUND OF THE SEARCH FEE

If applicable under Article 10 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.



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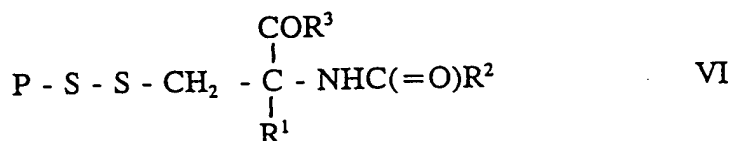


DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	CHEMICAL ABSTRACTS, vol. 106, no. 19, 11 May 1987 Columbus, Ohio, US; abstract no. 156843v, UBUKA, TOSHIHIKO ET AL: "Synthesis of disulfides related to glutathione and their detection in tissue" XP002052798 * page 728, column 2 * & GANRYU AMINOSAN, vol. 8, no. 1, 1985, JAPAN, pages 153-157, ---	1,4	A61K31/44 A61K38/05 A61K38/06 A61K38/07 A61K38/08 C07C321/14 C07C321/28 C07D213/70 C07H19/048 C07H21/00 C07K16/38 C08G69/04 C12N9/08
X	EP 0 482 766 A (KYOWA HAKKO KOGYO KK) 29 April 1992 * page 2 - page 3 * ---	1-4	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X	WO 91 16067 A (RES CORP TECHNOLOGIES INC) 31 October 1991 * claim 12 * ---	1-4	
X	STN INFORMATION SERVICE: FILE REG, XP002052828 * See RN 23130-02-1 * ---	1-5	C07D A61K C07H C12N C07C
X	PATENT ABSTRACTS OF JAPAN vol. 013, no. 056 (C-566), 8 February 1989 & JP 63 246382 A (KARUPISU SHOKUHIN KOGYO KK), 13 October 1988, * abstract * -----	12,14	
The supplementary search report has been drawn up for the claims attached hereto.			
Place of search MUNICH		Date of completion of the search 21 January 1998	Examiner Arias-Sanz, J
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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WHAT IS CLAIMED IS:

1. A compound of general formula VI



in which P is selected from the group consisting of peptides, proteins and oligonucleotides; R¹ is hydrogen, lower alkyl or aryl; R² is a lipid-containing moiety comprising a lipid group; and R³ is -OH, a lipid-containing moiety comprising a lipid group or an amino acid chain comprising one or 2 amino acids and terminating in -CO₂H or -COR².

2. A compound according to claim 1, wherein R¹ is hydrogen, R² is a lipid group and R³ is -OH.

3. A compound according to claim 1, wherein R¹ is hydrogen, R² is -CH₂CH₂CH(NH₂)CO₂H or -CH₂CH₂CH(NHCO-lipid)CO-lipid and R³ is -NHCH₂CO₂H or -NHCH₂CO-lipid in which at least one of R² and R³ comprises a lipid group.

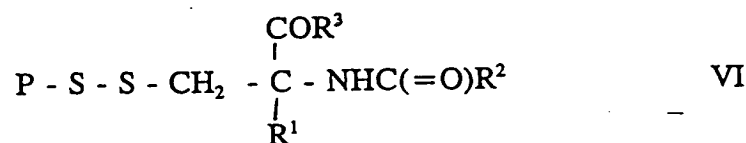
4. A compound according to claim 1, wherein said lipid group is a hydrophobic substituent comprising about 4 to about 26 carbon atoms.

5. A compound according to claim 4, wherein said lipid group is a hydrophobic substituent comprising about 5 to about 19 carbon atoms.

6. A method for increasing absorption of a sulfhydryl-group containing compound selected from the group consisting of peptides, proteins and oligonucleotides into mammalian cells, said method comprising:

forming from the sulfhydryl-containing compound a compound of general formula VI

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in which P is a moiety derived from the sulfhydryl-group containing compound selected from the group consisting of peptides, proteins and oligonucleotides; R¹ is hydrogen, lower alkyl or aryl; R² is a lipid-containing moiety; and R³ is -OH, a lipid-containing moiety or an amino acid chain comprising one or 2 amino acids and terminating in -CO₂H or -COR²; and

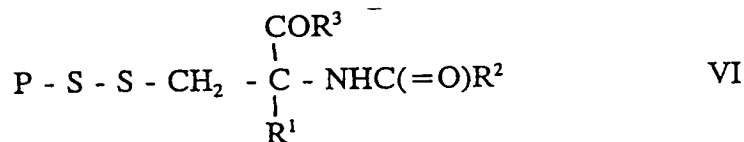
administering the compound of general formula VI to the cells.

7. A method according to claim 6, wherein R¹ is hydrogen, R² is a lipid group and R³ is -OH.

8. A method according to claim 6, wherein R¹ is hydrogen, R² is -CH₂CH₂CH(NH₂)CO₂H or -CH₂CH₂CH(NHCO-lipid)CO-lipid and R³ is -NHCH₂CO₂H or -NHCH₂CO-lipid in which at least one of R² and R³ comprises a lipid group.

9. A method for prolonging blood and tissue retention of a sulfhydryl-group containing compound selected from the group consisting of peptides, proteins and oligonucleotides into mammalian cells, said method comprising:

forming from the sulfhydryl-containing compound a compound of general formula VI



in which P is selected from the group consisting of peptides, proteins and oligonucleotides; R¹ is hydrogen, lower alkyl or aryl; R² is a lipid-containing moiety; and R³ is -OH, a lipid-containing moiety or an amino acid chain comprising one or 2 amino acids and terminating in -CO₂H or -COR²; and

administering the compound of general formula VI to the cells.

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10. A method according to claim 9, wherein R^1 is hydrogen, R^2 is a lipid group and R^3 is -OH.

11. A method according to claim 9, wherein R^1 is hydrogen, R^2 is $-\text{CH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$ or $-\text{CH}_2\text{CH}_2\text{CH}(\text{NHCO-lipid})\text{CO-lipid}$ and R^3 is $-\text{NHCH}_2\text{CO}_2\text{H}$ or $-\text{NHCH}_2\text{CO-lipid}$ in which at least one of R^2 and R^3 comprises a lipid group.

12. A compound of general formula V



in which A is an aromatic activating residue; R^1 is hydrogen, lower alkyl or aryl; R^2 is a lipid-containing moiety comprising a lipid group; and R^3 is -OH, a lipid-containing moiety comprising a lipid group or an amino acid chain comprising one or 2 amino acids and terminating in $-\text{CO}_2\text{H}$ or $-\text{COR}^2$.

13. A compound according to claim 12, wherein A is 2-pyridyl or 4-nitrophenyl.

14. A compound according to claim 12, wherein R^1 is hydrogen, R^2 is a lipid group and R^3 is -OH.

15. A compound according to claim 12, wherein R^1 is hydrogen, R^2 is $-\text{CH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$ or $-\text{CH}_2\text{CH}_2\text{CH}(\text{NHCO-lipid})\text{CO-lipid}$ and R^3 is $-\text{NHCH}_2\text{CO}_2\text{H}$ or $-\text{NHCH}_2\text{CO-lipid}$ in which at least one of R^2 and R^3 comprises a lipid group.

16. A method for forming a compound of general formula VI, comprising:
reacting a compound of general formula PSH, in which P is selected from the group consisting of peptides, proteins and oligonucleotides, with a compound of general formula V



in which A is an aromatic activating residue; R^1 is hydrogen, lower alkyl or aryl; R^2 is a lipid-containing moiety comprising a lipid group; and R^3 is -OH,

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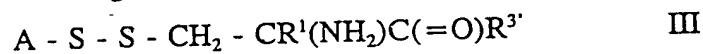
a lipid-containing moiety comprising a lipid group or an amino acid chain comprising one or 2 amino acids and terminating in $-\text{CO}_2\text{H}$ or $-\text{COR}^2$.

17. A method according to claim 16, wherein A is 2-pyridyl or 4-nitrophenyl.

18. A method according to claim 16, wherein R^1 is hydrogen, R^2 is a lipid group and R^3 is $-\text{OH}$.

19. A method according to claim 16, wherein R^1 is hydrogen, R^2 is $-\text{CH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$ or $-\text{CH}_2\text{CH}_2\text{CH}(\text{NHCO-lipid})\text{CO-lipid}$ and R^3 is $-\text{NHCH}_2\text{CO}_2\text{H}$ or $-\text{NHCH}_2\text{CO-lipid}$ in which at least one of R^2 and R^3 comprises a lipid group.

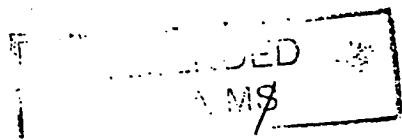
20. A compound of general formula III



in which $\text{R}^{3'}$ is $-\text{OH}$ or an amino acid chain comprising one or two amino acids and terminating in $-\text{CO}_2\text{H}$; A is an aromatic activating residue; and R^1 is hydrogen, lower alkyl or aryl.

21. A compound according to claim 20, wherein R^1 is hydrogen and $\text{R}^{3'}$ is $-\text{OH}$.

22. A compound according to claim 20, wherein R^1 is hydrogen and $\text{R}^{3'}$ is $-\text{NHCH}_2\text{CO}_2\text{H}$.



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23. Use of a compound of formula VI as set out in any of Claims 1-5 in manufacture of a medicament for prolonging blood and tissue retention of a sulfhydryl-group containing compound selected from the group consisting of peptides, proteins and oligonucleotides.

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 96 90 3690

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
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21-01-1998

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